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Intra-operative frozen section analysis of common iliac lymph nodes in patients with stage IB1 and IIA1 cervical cancer

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Abstract
Introduction To evaluate frozen section analysis of common iliac lymph nodes for developing the accuracy of para-aortic lymphadenectomy and detection of para-aortic lymph node metastasis in patients with stage IB1 and IIA1 cervical cancer treated by surgical intent.
Methods Three hundred and ninety-two patients with stage IB1 and IIA1 cervical cancer who underwent radical hysterectomy with pelvic and/or para-aortic lymphadenectomy were retrospectively analyzed. Among those patients, 183 (group A) underwent para-aortic lymphadenectomy when para-aortic lymph nodes were identified as suspicious by visualization and palpation. Other 209 patients (group B, underwent intra-operative frozen section analysis of common iliac lymph nodes) underwent para-aortic lymphadenectomy when frozen section analysis was positive, or para-aortic lymph nodes were identified as suspicious metastases by visualization and palpation.
Results We found 21 positive cases (10.0%) of 209 patients by frozen section examination, represented by 1 false negative (4.5%) and 0 false positive case. The specificity and the positive predictive value of frozen section examination were 100%; the negative predictive value was 99.5% (187/188). Overall, the metastasis rates of pelvic lymph node, common iliac lymph node, and para-aortic lymph node were 35.7, 10.2, and 3.3%, respectively. We found the dissection and metastasis rates of para-aortic lymph node in group B statistically significantly higher than group A (14.4% vs. 7.1%, for dissection rates of group B vs. group A, $P = 0.022$) (5.3% vs. 1.1%, for metastasis rates of group B vs. group A, $P = 0.021$).
Conclusion The frozen section analysis of common iliac lymph nodes can develop the accuracy of the para-aortic lymphadenectomy and metastasis rate of para-aortic lymph node in patients with stage IB1 and IIA1 cervical cancer.

Keywords Cervical cancer · Frozen section analysis · Common iliac lymph node · Para-aortic lymphadenectomy

Introduction

Cervical cancer is the second most common cancer and the third most common cause of cancer death in women worldwide [1, 2]. Radical hysterectomy (RH) with pelvic lymphadenectomy and/or para-aortic lymph node (LN) dissection is the surgical gold standard to treat patients with early-stage cervical cancer [3, 4]. But para-aortic lymphadenectomy in the surgical management still is a controversial issue because the incidence of para-aortic nodal involvement is very low in early-stage disease. Therefore, it may not be necessary to subject all patients to para-aortic lymphadenectomy, which requires additional surgical time

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and a certain amount of morbidity [5]. But some clinicians advocated that RH with pelvic and para-aortic LN dissection allows accurate surgical staging, allowing any adjuvant therapy to be more accurately targeted [6, 7].

The presence of clinically suspicious (abnormally enlarged or firm) pelvic or para-aortic lymph nodes or extra-cervical spread of tumor at the time of exploration were significant predictors of para-aortic metastases and indicated para-aortic lymphadenectomy should be done [8]. LN metastases in cervical cancer have the propensity to progress in an orderly fashion from parametrial, superficial obturator, external iliac, common iliac, para-aortic, to the supraclavicular region, and then to mediastinum. There is few para-aortic node metastasis when there is no evidence of common iliac lymph node metastasis [9]. Thus it is suggested that intraoperative evaluation of common iliac lymph node status might be helpful in defining the extent of pelvic lymphadenectomy and the need to proceed to para-aortic lymphadenectomy. Several evidences have been published about the diagnostic accuracy of frozen section analysis of pelvic lymph nodes in early-stage cervical cancer patients triaged to primary surgery; reported the negative predictive value and false negative rate were not satisfied [10–12]. And to our knowledge, there was few investigation of the diagnostic performance of frozen section analysis of common iliac lymph nodes in predicting the status of para-aortic lymph node and the need to excise the para-aortic lymph nodes.

This study was performed to evaluate frozen section analysis of common iliac lymph nodes for developing the accuracy of the para-aortic lymphadenectomy and detection of para-aortic lymph node metastasis in patients with stage IB1 and IIA1 cervical cancer treated by surgical intent.

Patients and methods

The medical charts of 392 patients with International Federation of Gynaecology and Obstetrics (FIGO) stage IB1 and IIA1 cervical cancer who underwent open RH (Piver types III) and bilateral pelvic lymphadenectomy and/or para-aortic LN dissection from November 2008 to May 2010 were retrospectively reviewed. Among those patients, 209 underwent frozen section analysis of common iliac lymph nodes during operation; if para-aortic lymph nodes were identified as suspicious by visualization and palpation (abnormally enlarged or firm) or positive frozen section analysis of common iliac lymph nodes,additional para-aortic lymphadenectomy up to inferior mesenteric artery wound be carried out during radical surgery. None of the patients received radiotherapy or chemotherapy before surgery. All radical surgeries were performed by gynecologic oncologists of the Department of Gynecologic Oncology at Zhejiang Cancer Hospital, Hangzhou, China.

All patients underwent RH and bilateral pelvic lymphadenectomy which was performed to remove all lymphatic tissues in the external iliac, internal iliac, common iliac, and obturator areas. The patients were composed by groups A and B. In group A (183 patients, did not undergo intraoperative frozen section analysis), if para-aortic lymph nodes were identified as suspicious by visualization and palpation (abnormally enlarged or firm), additional para-aortic lymphadenectomy up to inferior mesenteric artery wound be carried out during radical surgeries. Whereas in group B (209 patients, underwent intraoperative frozen section analysis of common iliac lymph nodes), if common iliac lymph nodes were intra-operatively defined as positive for tumor metastasis by frozen section analysis of common iliac lymph nodes or para-aortic lymph nodes identified as suspicious metastases by visualization and palpation, additional para-aortic lymphadenectomy up to inferior mesenteric artery was carried out. After surgical management, all tissues removed during surgery were histopathologically examined.

Records were reviewed for patients' age, body weight, clinical stage, tumor histology, length of hospital stay, hospital expenses, amount of surgical bleeding, operation time, complication, intraoperative results of frozen section analysis of common iliac lymph nodes, and histological status of pelvic and para-aortic lymph nodes. The performance of frozen section analysis of common iliac lymph nodes was assessed by calculating the false negative rate, the false positive rate, the specificity, the positive predictive value and the negative predictive value. Dissection and metastasis rates of para-aortic lymph node in two groups were compared to assess the value of frozen section analysis of common iliac lymph nodes.

Preoperative analysis

Clinico-pathological characteristics of the patients are summarized in Table 1. Clinical staging was performed according to FIGO 2009 classification: pretreatment evaluation consisted of a history and physical examination, biopsy and gynecologic examination. Abdomino-pelvic MRI or CT was performed to obtain full imaging analysis of para-aortic, and pelvic lymph nodes as well as abdominal organs. Chest X-ray or CT was also performed.

Frozen section analysis

Tissues removed from a specific common iliac lymph node station were intra-operatively analyzed by frozen section by a dedicated pathologist; all the lymph nodes identified by manual palpation (by size and gross appearance); lymph

Table 1 Clinical characteristics of the patients

Characteristics	Group A ($n = 183$)	Group B ($n = 209$)	P
Age, years	46.8 ± 9.9	47.4 ± 8.9	0.550*
Body weight, kg	57.0 ± 9.2	57.4 ± 9.7	0.641*
FIGO stage			0.961#
IB1	130 (71.0%)	148 (70.8%)	
IIA1	53 (29.0%)	61 (29.2%)	
Pathologic type			0.415#
Squamous cell carcinoma	159 (86.9%)	180 (86.1%)	
Adenocarcinoma	24 (13.1%)	27 (12.9%)	
Other	0	2 (1.0%)	
Length of hospital stay, d, $x \pm s$	18.2 ± 5.2	17.8 ± 4.4	0.482*
Hospital expenses, ¥, $x \pm s$	24,593.6 ± 4,865.7	28,656.0 ± 4,712.7	0.000*

* Student's t test

\# χ^2 test

nodes thicker than 5 mm were bisected and lymph nodes thicker than 1 cm were cut into several pieces, and the cut-surfaces were inspected. Four to eight frozen sections from each lymph node were cut at a distance of about 5 μm and stained with hematoxylin/eosin. The remaining tissue from the frozen section as well as the lymph nodes that did not undergo frozen section were fixed in 4% buffered formalin overnight, processed, and paraffin embedded; 24 serial sections per block were cut and stained with hematoxylin/eosin depending on the size of the lymph nodes. At time of data analysis, a repeated evaluation of the frozen section slides was performed and compared with the original frozen section report.

Statistical analysis

The correlation between frozen section and final pathology was calculated by false negative rate, false positive rate, specificity, positive predictive value and negative predictive value. Mean values between the two groups were compared by using the Student's t test. Frequency data between the groups were compared by using the χ^2 test. The data were analyzed by using SPSS software (Statistical Package for the Social Sciences, SPSS, Version 18.0, Chicago, IL). A value of $P < 0.05$ was considered to be statistically significant.

Results

A total of 392 patients with FIGO stage IB1 and IIA1 cervical cancer underwent open radical hysterectomy and bilateral pelvic lymphadenectomy and/or para-aortic lymph node dissection. The clinical characteristics of the patients are listed in Table 1; there were no statistically significant difference between the two groups, except for the hospital expenses. Among those patients, 209 underwent intraoperative frozen section analysis of common iliac lymph nodes. Common iliac lymph node metastases were found in 21 patients (10.0%) at frozen section examination and in 22 cases (10.5%) at definitive histological diagnosis. We found 21 in correct diagnoses at frozen section examination, represented by 1 false negative (False negative rate was 4.5%) and 0 false positive cases. The specificity and the positive predictive value of frozen section examination were 100%; the negative predictive value was 99.5% (187/188).

Three hundred and ninety-two patients all underwent radical hysterectomy and bilateral pelvic lymphadenectomy. In group A (183 patients), 13 patients (7.1%) had additional para-aortic lymphadenectomy when para-aortic lymph nodes were identified as suspicious by visualization and palpation. While in group B (209 patients, underwent intraoperative frozen section analysis of common iliac lymph nodes), 21 patients were defined as common iliac lymph node metastases by frozen section examination, and in other 189 patients, 9 patients' para-aortic lymph nodes were identified as suspicious by visualization and palpation, all 30 patients underwent additional para-aortic lymphadenectomy (14.4%). The excision rate of para-aortic lymph node in group B statistically significantly higher than group A (14.4% vs. 7.1%,group B vs. group A, $P = 0.022$) (listed in Table 2).

Records reviewed for patients' operation time, amount of surgical bleeding, complications are also presented in Table 2; there was no statistically significant difference of the amount of surgical bleeding between the two groups. Whereas the group B showed statistically longer operation time, much more complications than group A.

In all patients, the metastasis rates of pelvic lymph node, common iliac lymph node and para-aortic lymph node were 35.7, 10.2, and 3.3%, respectively. There was no significant difference between two groups in metastasis rates of pelvic lymph node and common iliac lymph node;

Table 2 Surgical and postoperative characteristics of the patients

Characteristics	Group A ($n = 183$)	Group B ($n = 209$)	P
Amount of surgical bleeding, ml ($x \pm s$)	322.5 ± 202.2	355.3 ± 184.6	0.094*
Length of operation, min ($x \pm s$)	161.9 ± 40.8	186.2 ± 44.8	0.000*
Complications	24 (13.1%)	50 (23.9%)	0.006#
Excision of para-aortic lymph node	13 (7.1%)	30 (14.4%)	0.022#
Metastasis of pelvic lymph node	47 (25.7%)	53 (25.4%)	0.941#
Metastasis of common iliac lymph node	18 (9.8%)	22 (10.5%)	0.031#
Metastasis of para-aortic lymph node	2 (1.1%)	11 (5.3%)	0.021#
Aortic metastasis during removal para-aortic lymph nodes	2 (15.4%)	11 (36.7%)	0.163#
Aortic metastasis during removal para-aortic lymph nodes in group A and positive frozen section patients in group B	2 (15.4%)	11 (52.4%)	0.016#

* Student's t test

\# χ^2 test

but the metastasis rate of para-aortic lymph node in group B statistically significantly higher than group A (5.3% vs. 1.1%, group B vs. group A, $P = 0.021$). In group A, during 13 patients underwent para-aortic lymphadenectomy, 2 cases (15.4%) were defined as para-aortic lymph node metastasis by histopathologically examination; while in group B, 11 patients (36.7%) were defined as para-aortic lymph node metastasis during 30 cases undergoing para-aortic lymphadenectomy. Whereas the 11 patients all were found in the 21 patients who were defined as common iliac lymph node metastases by frozen section examination and underwent para-aortic lymphadenectomy in group B; during these 21 patients, the para-aortic lymph node metastasis rate ascended to 52.4% which statistically significantly higher than group A (52.4% vs. 15.4%, group B vs. group A, $P = 0.016$) (Table 2).

Discussion

In our investigation, 21 of 209 patients undergoing intra-operative frozen section analysis of common iliac lymph nodes were indicated as common iliac lymph node metastases by frozen section examination. We found 21 all in correct diagnoses at frozen section examination, represented by 0 false positive case and 1 false negative (false negative rate was 4.5%). The specificity and the positive predictive value of frozen section examination were 100%; the negative predictive value was 99.5% (187/188).

In several reports, the accuracy of frozen section analysis of pelvic lymph nodes had been investigated in early-stage cervical cancer, which had reported false negative rates of 16.9–35.7% [10–12]. Bader et al. [10] reported a false negative rate of 16.9% in a series of 53 patients with no false positive case. The sensitivity and negative predictive value of frozen section examination were 83 and 91% at primary surgery. Scholz et al. [11] investigated 96 patients who underwent intra-operative frozen section examination, and node metastases were found in 29 patients (30%). Final histopathological results identified an additional seven patients with node metastases for a false negative rate of 19%. The specificity and the positive predictive value (PPV) of frozen section examination were 100%; the negative predictive value was 90% (60/67). In a series of 123 locally advanced cervical cancer patients, Mitchell et al. [12] found the false negative rate, specificity, sensitivity, negative predictive value (NPV), and PPV of frozen section examination of pelvic lymph nodes were 35.7, 98.2, 64.3, 95.5, and 81.8%. Our results of the specificity and the positive predictive value of frozen section examination are consistent with those other studies; but the false negative rate (4.5%) is lower. The most important factor maybe the tissues undergoing intra-operative frozen section of our investigation were only common iliac lymph nodes, whereas other reports were all the pelvic lymph nodes. Only common iliac lymph node tissues undergoing frozen section are smaller than all pelvic lymph nodes tissues and would decrease the difficulty of palpating and dissecting the lymph nodes tissue for frozen section examination by pathologists and elevate the examination rate of common iliac lymph nodes.

Independent risk factors for para-aortic nodes involvement include multiple pelvic lymph node metastasis and common iliac node metastasis, suggesting there is a sequential method of metastasis to the subsequent lymph node chains [13]. It has been found in a number of studies that the risk of para-aortic node metastasis alone is extremely rare in cervical cancer [5, 8, 9, 13]. The results of frozen section examination of common iliac lymph nodes can influence the surgical management of patients with cervical cancer. Clinically, the indication for para-aortic lymphadenectomy is often based on the suspicious pelvic or para-aortic lymph nodes by visualization and palpation at the time of exploration [8]. Additional intra-operative frozen section analysis of common iliac lymph nodes is another useful predictor suggested by our results. The excision rate of para-aortic lymph node in group B (additional intra-operative frozen section analysis of common

iliac lymph nodes) statistically significantly higher than group A (14.4% vs. 7.1%, group B vs. group A, $P = 0.022$). The metastasis rates of para-aortic lymph node in group B statistically significantly higher than group A (5.3% vs. 1.1%,group B vs. group A, $P = 0.021$); while there was no significant difference between two groups in metastasis rates of pelvic lymph node and common iliac lymph node.

Para-aortic nodal involvement is an important determinant of prognosis and treatment; especially for the radiation treatment plan [14]. Pathologic evaluation of node-bearing tissue remains the standard for the evaluation of nodal metastasis in patients with cervical cancer undergoing radical hysterectomy. However, para-aortic lymphadenectomy requires additional surgical time and a certain amount of morbidity [5]. In our result, there was no statistically significant difference of the amount of surgical bleeding between the two groups, whereas the group B showed statistically longer operation time, much more complications than group A which may be influenced by higher excision rate of para-aortic lymph node in group B. Therefore, it is important for patients to have accurately para-aortic lymphadenectomy. The para-aortic lymph node metastasis rate in the patients had positive frozen section examination of common iliac lymph nodes was 52.4% which is statistically significantly higher than that of group A (52.4% vs. 15.4%,group B vs. group A, $P = 0.016$); suggesting that intra-operative frozen section examination of common iliac lymph nodes can be used to develop the accuracy of the para-aortic lymphadenectomy.

Although lymph node status is not part of the FIGO staging, it is an important determinant of prognosis and treatment, especially for the radiation treatment plan [14, 15]. Following surgery, patients with LN metastasis are administered effective adjuvant therapy, consisting of radiation therapy (RT) or concurrent chemo-radiation therapy (CCRT), to decrease recurrence and improve survival [16]. In the presence of para-aortic nodal involvement, adjuvant therapy with extended field radiotherapy (EFRT) is often chosen [16, 17], however, high rates of complications and morbidity may occur [17–19]. So it is important to accurately determine the status of para-aortic lymph nodes, in order to provide accurate prognostic information and determinant of treatment. Pathologic evaluation of node-bearing tissue remains the standard for evaluation of nodal metastasis in patients with cervical cancer undergoing radical hysterectomy. Intra-operative frozen section examination of common iliac lymph nodes can develop the accuracy of the para-aortic lymphadenectomy. As a result, it can provide more accurate prognostic information and adjuvant therapy, while avoiding extended radiation in those with negative para-aortic nodes prevents toxicity.

In conclusion, it is suggested that frozen section examination of common iliac lymph nodes can elevate the excision and the metastasis rate of para-aortic lymph node and can improve the accuracy of the para-aortic lymphadenectomy and postoperative adjuvant therapy in patients with stage IB1 and IIA1 cervical cancer treated by surgical intent, which allows a more individualized treatment for cervical cancer patients.

Conflict of interest None.

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